II. Remarks

A. Amendments to the Claims and Formal Matters

Claims 62, 66-71 and 75-83 and 85 are pending and under active consideration in the application. Claims 1-61, 63-65, 72-74, 84 and 86 were previously canceled. Claims 62, 66, 75 and 82 are amended. Claims 83 and 85 are canceled without prejudice to pursuing these claims in a continuing application. Claims 87-94 are new. Upon entry of these amendments, claims 62, 66-71, 75-82 and 87-94 will be pending and under active consideration. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application.

Claim 62 is amended to recite that the isolated human IFNAR2 polypeptide comprises the sequence of SEQ ID NO: 2, support for which may be found in claim 66 as filed.

Claim 66 is amended to recite that the claimed polypeptide "consists essentially of the sequence of SEQ ID NO: 2", support for which may be found in the specification at paragraph [0061]. All references to the specification made herein will be made with reference to the substitute specification, filed with Applicant's Preliminary Amendment of June 30, 2004.

Claim 82 is amended to delete the phrase "and optionally an IFN antagonist."

Support for new claim 87 may be found in the specification at paragraph [0021].

Support for new claim 88 may be found in claims 42, 44 and 46 as filed.

Support for new claims 89, 90 and 91 may be found in claims 47, 45 and 43, respectively, as filed.

Support for new claim 92 may be found in claim 40 as filed.

Support for new claim 93 may be found in claim 39 as filed.

Support for new claim 94 may be found in claim 48 as filed.

B. Patentability Rejections

1. The Rejections Under 35 U.S.C. §112, First Paragraph – Written Description – Should be Withdrawn

At page 3 of the Final Office Action, the Examiner maintained the rejection of claims 62, 67-71, 75-83 and 85 under 35 U.S.C. §112 as allegedly failing to comply with the written description requirement. Examiner alleged that Applicant described only one species of IFNAR2 polypeptide and therefore is not entitled to the genus. In response, Applicant amended the claims to be directed to human IFNAR2 polypeptides. *See* Applicant's Response to Final Office Action, filed September 28, 2006.

In the Advisory Action, the Examiner maintains the rejections of claims 62, 67-71, 75-83 and 85 under 35 U.S.C. §112 as allegedly failing to comply with the written description requirement. Specifically, the Examiner alleges that the pending claims "continue to read on other alternatively spliced forms of IFNAR2, including membrane bound and cytoplasmic forms." *See* Advisory Action, page 2.

Applicant cancels claims 83 and 85. Applicant amends claim 62 to recite that the claimed polypeptide comprises the sequence of SEQ ID NO: 2. Thus, claim 62, as amended, is co-extensive with previously pending claim 66. Previously pending claim 66 was not rejected by the Examiner under 35 U.S.C. §112 as failing to comply with the written description requirement. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claim 62 under 35 U.S.C. § 112, first paragraph. Applicant also respectfully requests reconsideration and withdrawal of the rejections of claims 67-71 and 75-82, as each of these claims depends from and consequently incorporates all the limitations of claim 62.

According to the Guidelines for the Examination of Patent Applications under the 35 U.S.C. § 112, first paragraph, "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111 (the "Written Description Guidelines"), the written description requirement can be met by showing "that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics [such as] complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *See* Written Description Guidelines at page

1106. The Federal Circuit, in *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 USPQ2d 1602 (Fed. Cir. 2002), adopted this portion of the Written description Guidelines. The instant specification discloses the synergistic effect of alanine substitutions at positions 78 (histidine) and 100 (asparagine) of the human IFNAR2 extracellular domain on binding to TGFβ. According to the specification, IFNAR2 is the beta subunit of the type I IFN receptor and exists in three forms: two membrane bound (β_S and β_L) and one soluble (p40). *See* specification, paragraphs [0006]-[0008]. IFNAR2 β_S and β_L are disclosed as having "identical" extracellular domains and soluble p40 IFNAR2 is disclosed as "encompass[ing] almost the entire extracellular domain of the IFNAR2 subunit." Each of these alternatively spliced IFNAR2 forms have been shown to bind IFNβ through the extracellular domain (see paragraphs cited *supra*). Human IFNAR2 extracellular domain, demonstrated by the working examples to exhibit synergistically increased affinity for IFN-β when alanine is substituted for histidine at position 78 and asparagine at position 100, is a common attribute of every member of the claimed genus and constitutes a substantial portion of every member of the claimed genus. Accordingly, there is not substantial variation among the species within the claimed genus. The structure to function relationship disclosed by the specification, specifically that the claimed mutations within the extracellular domain result in synergistic binding to TGFβ, is sufficient to demonstrate possession of the claimed genus to one of ordinary skill in the art, especially in view of the fact that each wild-type IFNAR2 form binds TGFβ (an extracellular ligand) through its extracellular domain.

Thus, one of ordinary skill in the art, based on the above-noted explicit descriptions provided by the specification, would understand that because the extracellular domain of IFNAR2 is the portion that interacts with IFNβ, that the teachings of the instant invention apply to alternatively spliced IFNAR2 isoforms and accordingly will understand that Applicant possessed this aspect of the invention at the time the Application was filed. Based on the foregoing, Applicant respectfully requests the Examiner withdraw the rejection of claims 62, 67-71 and 75-82 for lack of written description.

2. The Rejections Under 35 U.S.C. §112, First Paragraph – Enablement – Should be Withdrawn

a. Claims 62, 66-71 and 75-82

At page 6 of the Final Office Action, the Examiner maintained the rejection of claims 62, 66-71 and 75-82 under 35 U.S.C. §112 for an alleged lack of enablement. The Examiner based this rejection on his allegation that the claims "broadly encompass isolated and mutated polypeptide sequences of numerous variants of the type I IFN receptors, such as membrane bound, cytoplasmic or soluble forms." In response, Applicant amended the claims to be directed to "human" IFNAR2 polypeptides and pointed out to the Examiner that the pending claims were directed to IFNAR2 polypeptides specifically and not to "type 1 IFN receptors" generally, which would include unclaimed IFNAR1 subunits. *See* Applicant's Response to Final Office Action.

In the Advisory Action, the Examiner maintains the rejections of claims 62, 66-71 and 75-82 under 35 U.S.C. §112 for an alleged lack of enablement. Specifically, the Examiner alleges that "the aforementioned issues regarding receptor types also apply to this rejection." *See* Advisory Action, page 2.

Applicant amends claim 62 to incorporate the limitation of previously pending claim 66 that the claimed polypeptide comprises the sequence of SEQ ID NO: 2. Applicant amends claim 66 to recite that the claimed polypeptide consists essentially of the sequence of SEQ ID NO: 2. Applicant amends claim 82 to delete reference to "an IFN antagonist."

The prior art teaches that IFNAR2 is the beta subunit of the type I IFN receptor and that, in humans, IFNAR2 exists in three forms: two membrane bound (β_S and β_L) and one soluble (p40). The prior art also teaches that IFNAR2 β_S and β_L have "identical" extracellular domains and soluble p40 IFNAR2 consists of nearly the entire extracellular domain of the IFNAR2 subunit. Importantly, the prior art teaches that each of these alternative IFNAR2 alternative splice variants bind IFNβ through the extracellular domain. The claimed genus, comprising polypeptides comprising the sequence of SEQ ID NO: 2 wherein alanine substitutions at positions 78 (histidine) and 100 (asparagine) result in synergistic binding to TGFβ, can be created and identified without undue experimentation by one of ordinary skill in the art using standard mutagenesis techniques,

as described by the specification at paragraphs [0088]-[0089] and the assay provided by the specification for identifying each member of the genus which synergistically enhances binding. *See, e.g.*, specification, paragraph [0090].

The instant specification, as noted *supra*, discloses the synergistic effect of alanine substitutions at positions 78 (histidine) and 100 (asparagine) of the human IFNAR2 extracellular domain on binding to TGFβ. Example 2 describes the generation of the IFNAR2 extracellular domain polypeptide comprising said mutations. Example 5 describes the thermodynamic and kinetic analysis of the interaction between TGFβ and the IFNAR2 extracellular domain mutant and wild type polypeptides and discloses that the affinity of IFNβ to the mutant polypeptide is over 50-fold higher than to that of the wild type protein. As noted *supra*, each of the rejected claims contains the limitation that the claimed polypeptide comprises the sequence of SEQ ID NO: 2, i.e., the extracellular portion of IFNAR2 responsible for binding to TGFβ found in each of the three human IFNAR2 polypeptides identified.

One of ordinary skill in the art understands that protein domains are to a large extent independent in terms of their structure, function and folding behavior. This is particularly the case for extracellular protein domains, which one of ordinary skill in the art understands may properly be conceptualized as distinct folding units. The extracellular domain of human IFNAR2 has been shown to be a stable fully active protein with a stoichiometry of binding IFNα2 of 1:1, identical to that of IFNAR2 β_S and β_L and soluble p40 IFNAR2. *See* specification, paragraph [0013]. Applicant respectfully submits that one of ordinary skill in the art, in light of the foregoing, would understand that the exemplification of the mutated human IFNAR2 extracellular domain provides the predictability necessary to enable the full scope of the claims. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejections for lack of enablement.

b. Claims 83 and 85

At page 7 of the Final Office Action, the Examiner maintained the rejection of claims 83 and 85 under 35 U.S.C. §112 for an alleged lack of enablement because, according to the Examiner, "[t]he specification fails to provide a description of what constitutes a therapeutically effective amount of a composition comprising the IFNAR2 mutated polypeptide." Applicant, in the Response to the Final Office Action, cited

portions of the specification that define a "therapeutically effective amount" as an amount that, when administered, "results in modulation of the biological activity of IFNβ" and which teach a variety of factors upon which "[t]he dosage administered...may vary."

In the Advisory Action, the Examiner maintains the rejection of claims 83 and 85 under 35 U.S.C. §112 for an alleged lack of enablement. According to the Examiner "Applicants have failed to address the issues set forth in the final office action, regarding the combined administration of the receptor and an IFN antagonist, in the context of their different properties as protagonist and antagonist."

Applicant amends claim 82 to delete reference to "an IFN antagonist." Applicant cancels claims 83 and 85 and adds new claims 87-92. Applicant respectfully submits that new claims 87-92 are enabled by the specification.

As a preliminary matter, Applicant respectfully disagrees with Examiner's characterization of Hertzog *et al.* (PCT Publication No. WO 00/24417) as summarizing the "state of the prior art." *See* Non-Final Office Action, mailed November 21, 2005, page 9. Applicant respectfully submits that European Patent No. EP1037658 B1 (published June 5, 2002)(hereinafter, the "'658 patent"), reference B3 on Form PTO/SB/08A of Applicant's Information Disclosure Statement, mailed February 8, 2005, and considered by the Examiner on November 7, 2005, is more pertinent to the state of the prior art.

1) New Claims 88-91 are Enabled

The instant specification teaches that mutated IFNAR2 polypeptide may be used as a carrier protein for IFNβ in order to enhance IFNβ's bioavailability, enhance its potency and prolong its *in vivo* effects. *See* specification, paragraph [0040]. According to the specification, the mutated IFNAR2 polypeptide may be administered alone to stabilize and enhance the effects of endogenous IFNβ or may be administered as a complex with exogenous IFNβ. *See* specification, paragraph [0036]. Whether administered alone or as a complex with IFNβ, "considerably lower amounts [of mutated IFNAR2 than of wild type IFNAR2] will be required to accomplish its carrier activity." *See* specification, paragraph [0034]. Consequently, a lesser quantity of IFNβ can achieve

the same biological effect when administered as a complex with mutated IFNAR2 (with a corresponding reduction in side effects) and a lesser quantity of mutated IFNAR2 need be administered alone to stabilize and enhance the effects of endogenous IFNβ. The administration of wild type IFNAR2 alone and as a complex with IFNβ is described throughout the '658 patent.

For each of these applications, a therapeutically effective amount of mutated IFNAR2 is an amount sufficient to result in "some portion of [IFNβ] available for curative activity (20%) and some amount of [IFNβ] bound to the [mutated IFNAR2] and protected (about 80%)" (*see* paragraph [0030]). For the claimed polypeptides, the specification teaches that the desired result is achieved at a concentration of "about 0.24 nM…equivalent to 6 μg/Kg)" of mutated IFNAR2 polypeptide (see paragraph [0032]). A simulation of the concentration of bound and free IFNβ in the presence of different concentrations of mutated IFNAR2 based on the law of mass action and a Kd of 3nM (tested by reflectometric interference spectroscopy) is provided in Figure 1. The simulation demonstrates that in order to achieve 20% free IFNβ (10 pM or 100 Units) and 80% bound, only about 0.24 nM of the mutated IFNAR2 polypeptide is required compared to 12.5 nM of wild type IFNAR2.

The essential accuracy of the simulation depicted in Figure 1 is verified in Example 7 in which a constant concentration of IFNβ (10 pM) was mixed with varying concentrations of, *inter alia*, mutated IFNAR2 polypeptide and the resulting mixture added to WISH cells (human amniotic cells). The WISH cells were then challenged with vesicular somatitis virus and free IFNβ (representing anti-viral activity) was monitored as the degree of cell survival over a 24-hour incubation. The results demonstrate that 80% of IFNβ is bound at a concentration of 0.4 nM of mutated IFNAR2 polypeptide while about 12.5 nM of wild type IFNAR2 is required to achieve the same result (a more than 30-fold higher concentration).

As noted *supra*, a "therapeutically effective" amount of a composition comprising mutated IFNAR2 polypeptide, according to the specification, is one which results in modulation of the biological activity of IFNβ, for example by ehancing its stability, enhancing its potency, or prolonging its *in vivo* effects. As the specification makes clear,

that result is optimally obtained at concentrations of 0.24 nM – 0.4 nM of mutated IFNAR2 polypeptide. Adjustments and manipulation of this range may be required depending on a variety of factors such as route of administration, physical characteristics of the individual patient, the extent of symptoms, concurrent treatments and the like. Determination of dosage is routine in the art and such adjustments are well within the ability of those skilled in the art.

Finally, the specification discloses that IFNβ acts through IFN type I receptor to induce biologic effects such as anti-viral, anti-tumor and immune modulation. *See e.g.*, specification, paragraph [0006]. Specific examples of diseases that may be treated with compositions of the instant invention by virtue of IFNβ's anti-viral, anti-tumor and immune modulation effects are listed by the specification at paragraphs [0073], [0074] and [0072], respectively. One of ordinary skill in the art understands that compositions of the instant invention are effective for treating any disease that responds to modulation of bioavialable IFNβ. For example, intrathecal administration of IFNβ has been demonstrated to be effective in reducing the symptoms of multiple sclerosis (MS). *See* specification, paragraph [0010]. The anti-viral capacity of IFNβ is well known in the art and is demonstrated by the instant specification at Example 7. The anti-tumor capacity of IFNβ is demonstrated, e.g., in the '658 patent at paragraphs [0010] and [0116]-[0119].

In view of the foregoing, Applicant respectfully submits that new claims 88-91 are fully enabled.

2) New Claim 94 is Enabled

Where the goal is to prevent the biological activity of an endogenous interferon such as IFNβ, mutated IFNAR2 polypeptide can act as a carrier molecule for an antagonist of the IFN receptor, so long as the antagonist binds the mutated IFNAR2 receptor and has antagonistic activity on the IFN receptor. *See* specification, paragraph [0063]. Selecting a "therapeutically effective" amount of a composition comprising mutated IFNAR2 polypeptide and an antagonist is well within the skill of the ordinary artisan and may be determined without undue experimentation. For example, one of ordinary skill in the art can easily determine the affinity of the antagonist for the mutated

IFNAR2 receptor and use the laws of mass action to determine a therapeutically effective concentration of mutated IFNAR2 receptor and antagonist. Accordingly, Applicant respectfully requests that the rejection for lack of enablement be withdrawn.

3. The Rejections Under 35 U.S.C. §103(a) Should be Withdrawn

a. Claims 62, 66-71 and 75-76

At page 8 of the Final Office Action, the Examiner maintained the rejection of claims 62, 66-71 and 75-76 under 35 U.S.C. §103(a) over Piehler *et al.* ("Piehler"), which the Examiner characterized as (i) describing the effects of individual mutations at positions His 78 and Asp 100; (ii) providing the motivation to simultaneously mutate His 78 and Asp 100; and (iii) providing a reasonable expectation of success. Applicant, in the Response to the Final Office Action respectfully submitted that the Examiner failed to take into account secondary considerations of non-obviousness.

The Examiner, in the Advisory Action, maintains the rejections of claims 62, 66-71 and 75-76 under 35 U.S.C. §103(a) over Piehler because, according to the Examiner, "arguments of counsel cannot take the place of evidence in the record."

Applicant reminds the Examiner that secondary considerations such as unexpected results, must be considered in every case in which they are present. *See MPEP* § 2141. The Federal Circuit in *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997), cited by the Examiner in the Advisory Action, held that mere attorney argument, unsupported by factual evidence, is insufficient to establish unexpected results. The Examiner alleges that no evidence of synergistic results is contained in the record. Applicant respectfully disagrees and emphasizes that the facts supporting a determination of synergy are found within the four corners of the instant specification and do not constitute mere attorney argument.

The instant specification at paragraph [0095], states that "the single mutations in INFAR2 increase the affinity of the complex from 4.6 up to 7.3 fold, while the double mutation [H78A/N100A] causes a synergistic effect" (emphasis added). This is summarized on Table 4 wherein the claimed double mutant H78A/N100A is shown to possess an "above 50-fold" increase in affinity for TGFβ compared to wild type. The single mutant (H78A) possesses only a 4.6-fold increase in affinity for TGFβ over wild type and the single mutant (N100A) possesses only a 7.3-fold increase in affinity for TGFβ over wild type. This is factual evidence and does not constitute attorney argument. Piehler fails to teach or suggest such a result. According to MPEP § 716.02(a), a demonstration of synergy is sufficient to overcome a *prima facie* case of obviousness

where the results obtained are greater than those which could have been expected from the prior art to an unobvious extent and the results are of significant, practical advantage.

The Examiner, at page 8 of the Final Office Action, alleged that "Piehler expected a synergistic effect for the double mutation." To support this allegation, the Examiner cited a statement in Piehler which the Examiner removed from its proper context. The statement cited by the Examiner, in context, reads: "the phenotype of a H78, N100 double mutation in ifnar2 [should] have about 20-fold tighter binding for IFNβ compared to IFNα2" (emphasis added). Thus, Piehler's statement is not comparing the affinity of H78A/N100A for IFNβ to that of wild type IFNAR2; rather, Piehler's statement compares the relative affinity of H78A/N100A for IFNβ and IFNα. In light of Piehler's disclosure that the affinity of H78A for IFNα is reduced more than two-fold, a nearly 20-fold tighter binding of IFNβ compared to IFNα is the expected result in the absence of synergy between the mutations.

Applicant respectfully submits that Piehler, a reference of record, not only fails to teach or suggest any synergistic effect of a double mutation on IFNAR2 affinity for TGFβ, Piehler actually teaches that such a result is unexpected. According to Piehler, substituting alanine for histidine at position 78 (H78A) and asparagine at position 100 (N100A) of IFNAR2 decreases the dissociation rate constant for IFNβ by almost twofold and fourfold respectively. The change in the free energy of binding IFNβ is disclosed as -1.9 kJ/mole for H78A and -3.1 kJ/mole for N100A. According to Piehler, and as is known in the art, the change in free energy for a multiple mutant should equal the sum of energy changes of the individual single mutations. Thus, for the claimed double mutant H78A/N100A, a change in free energy of binding IFNβ of 5.0 kJ/mole is the expected result. According to the formula (5) of Piehler, this corresponds to an expected 8-fold increase in affinity of H78A/N100A for IFNβ. The present specification, however, teaches that H78A/N100A exhibits a greater than 50-fold increase in affinity – **more than six-times the expected result**. Applicant points out to the Examiner that the calculated 8-fold increase in affinity of H78A/N100A is based on sound scientific principles of fact and does not constitute, as Examiner alleges, mere attorney argument.

Applicant reminds Examiner that according to *In re Soni*, 54 F.3d 746, 750, 34 USPQ.2d 1684, 1687 (Fed. Cir. 1995), where the evidence relied upon by Applicant to show unexpected results is in the specification to which Applicant has attested, a declaration according to 37 C.F.R. § 1.132 is unnecessary. Applicant has pointed out to the Examiner a site in the specification which explicitly discloses that substitution of both the histidine at position 78 and the asparagine at position 100 of the IFNAR2 extracellular domain are synergistic with regard to affinity for IFNβ. Applicant has also pointed out to the Examiner that Piehler, a reference of record, teaches that such a synergistic result could not have been unexpected. In light of the unexpected, claimed synergistic increase, no indication of which is disclosed by Piehler and which could not have been obvious to the ordinary artisan, Applicant respectfully requests that the rejection for obviousness be reconsidered and withdrawn.

b. Claims 77-81

At page 9 of the Final Office Action, the Examiner maintains his rejection of claims 77-81 under 35 U.S.C. §103(a) over Piehler and Campbell *et al.* ("Campbell"). As discussed above, Piehler fails to teach or suggest the synergistic effect of the claimed double mutant H78A/N100A. Campbell, characterized by the Examiner as describing fusion protein constructs containing the hGH signal peptide in place of the native signal sequence of proteins, does nothing to remedy the defect of Piehler. Accordingly, Applicant respectfully requests that the rejection for obviousness be reconsidered and withdrawn.

C. Conclusion

In view of the above amendments and remarks, Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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